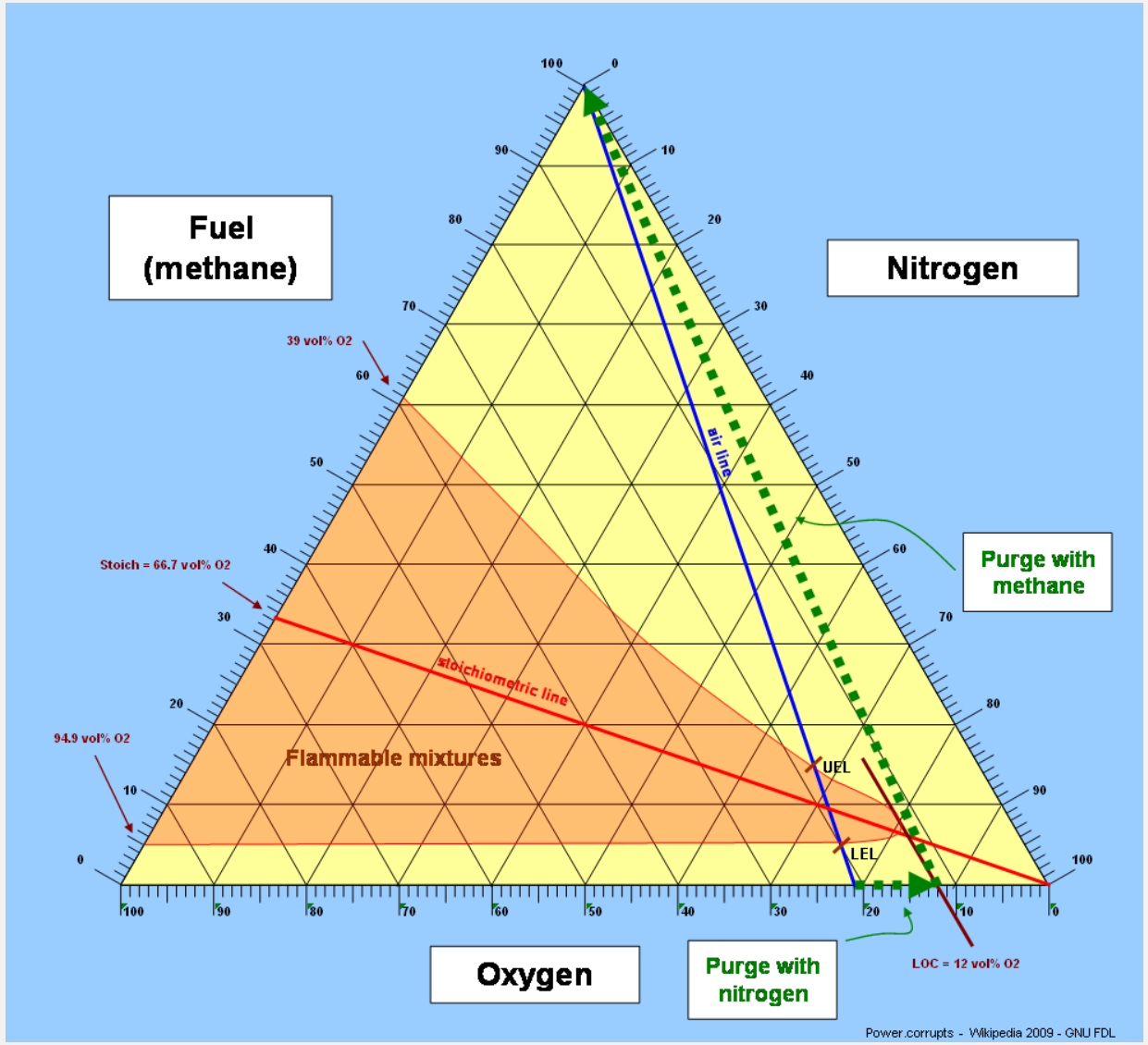
TECHNICAL SERVICES DEPT

ROAD MAP & MATURITY MATRIX



Limiting Oxygen concentration

The **limiting oxygen concentration** (**LOC**), al so known as the **minimum oxygen concentration** (**MOC**),, i s defined as the limiting concentration of oxygen below which combustion is not possible, independent of the concentration of fuel.

PILLARS FOR PERFORMANCE, CONSISTENCY AND IMPROVEMENT

Performance & Consistency comes with right Measurement, design Control and removal of dependencies

History is What is Written.

Build Trust and transparency

The idly batter story

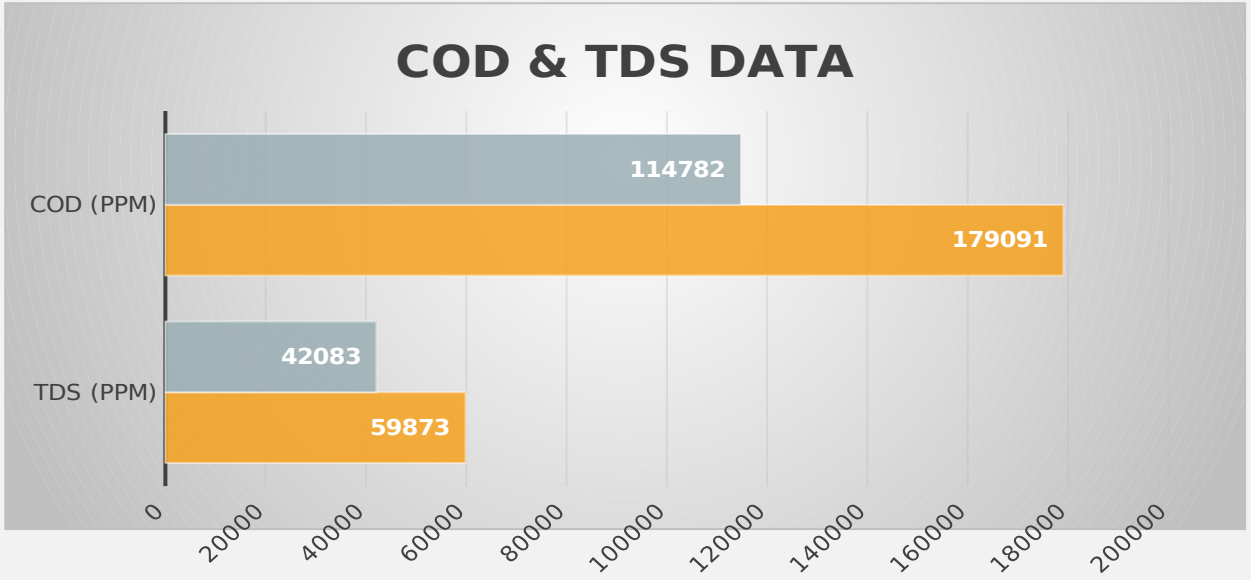
Uniform & consistent communication

Do what you write and write what you do

Measure, analyse, Improve and control.

When you See right, you think right.

ARE WE AT LOSS?



- The amount of solvent lost per day – 10 kl @ Rudraram and almost 50 kl across all sites.
- 70,000 ppm to stripper, 30,000 ppm to MEE & 6000 ppm to Bilogical treatment plant and Bio outlet is 250 ppm- This is the industry standard.
- The recovery of this solvent & sale as spent can recover the CapEx in less than 2 year and also cover the OpEx.
- The presence of high COD will also damage the cooling towers and intern the reactors.
- Infrequent blow down in cooling tower, can reduce TSD in effluent, but it can lead to increase in TDS in cooling tower water, which can impact the reactor and heat exchanger heat efficiency.

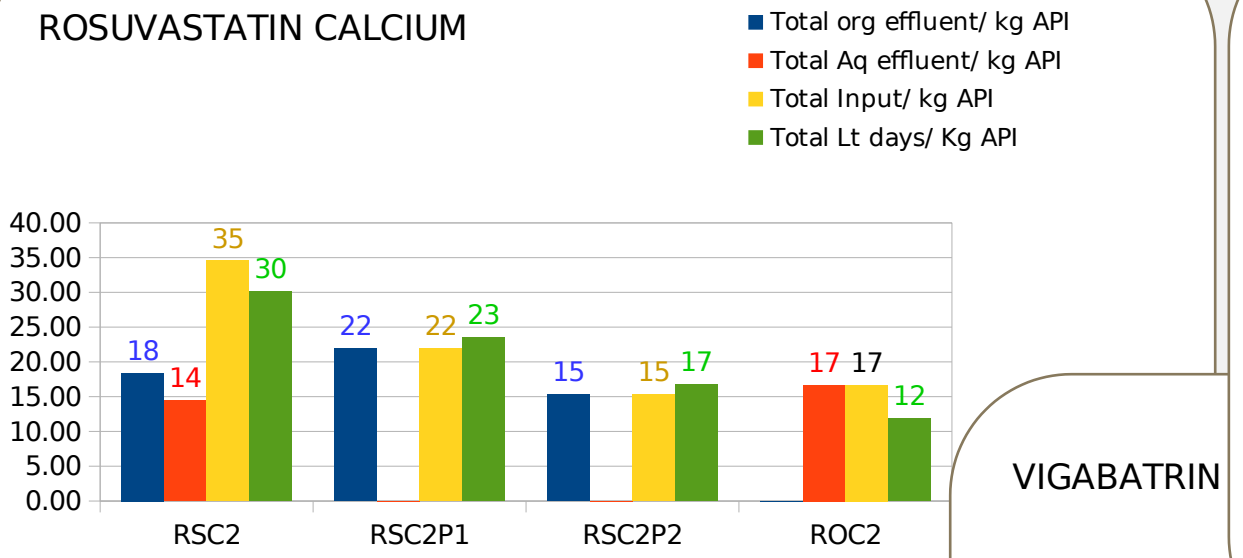
ARE WE AT LOSS?

	Rosuvastatin	Vigabatrin	Pragabalin
Total Over head cost @ Unit-01/month	19 Cr	19 Cr	18 Cr
Total volumetric capacity	1352 Kl	1352 Kl	1290 KL
Over head Cost/ KL	5019 Rs	5019 Rs	4983 Rs
Volumetric capacity used	98 (without MLPL)	133 Kl	504 Kl
Total reactor volume consumed/ month	2744 KL month	3724 KL month	14112 Kl Month
Quantity produced in Month	7800 Kg	2400	30000 Kg
KL Used/Kg API	0.352 Kl month/kg	1.552 kl month/kg	0.470 Kl month/Kg
Estimated over head cost	1766 Rs / Kg API	7788 Rs/ kg API	2344 Rs / Kg Intermediate
RMC	20000 Rs	29400 Rs	3334 RS
% OH to RMC		26%	70%

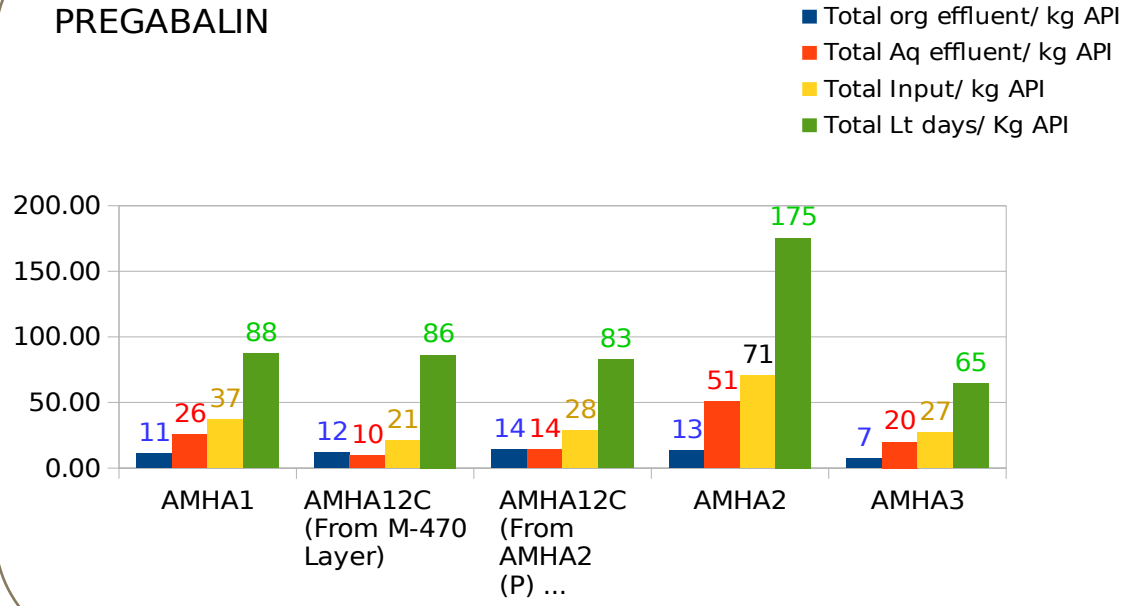
* Industry standard is 10 – 15% of site OH and another 5 % from sales and marketing .

PROCESS PERFORMANCE INDEX

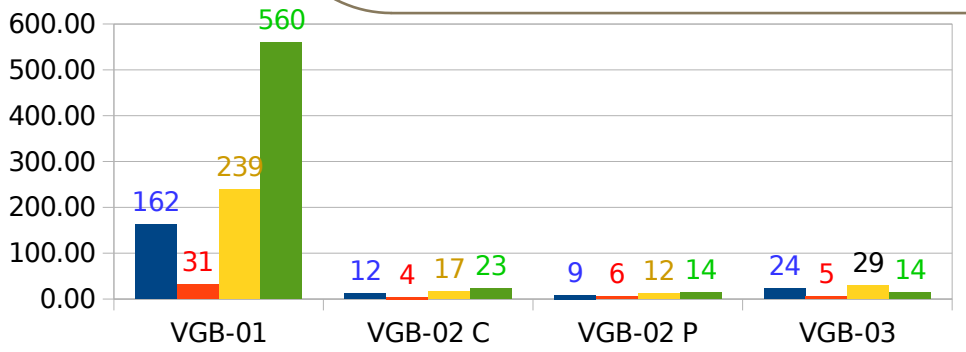
ROSUVASTATIN CALCIUM



PREGABALIN



VIGABATRIN



Etifoxine Manganese Dioxide Charging Safe Handling

MSN Organics Private Limited

oxine is manufactured in D-Block campaign basis product (600kg /annum) with revenue 1.5Cr, currently Manganese Dioxide being used for cyclization by inse

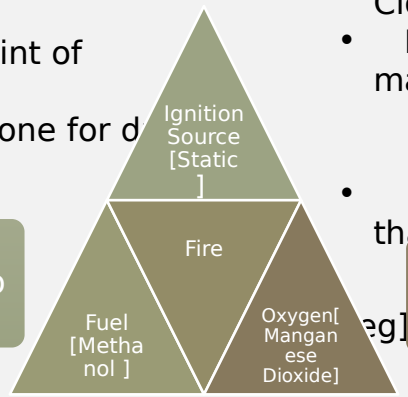
Proposal

ing Procedure : Currently the Manganese Dioxide [52kg] shall be charged in to reactor in 500L methanol through Manhole with Scoop with Nitrogen blanket

Current Procedure :

- Charging of material through manhole , Risk of Air exposure.
- No Positive Nitrogen atmosphere
- Charging of Manganese dioxide above the flash point of methanol
- Particle size of Manganese dioxide is 44 micron , prone for d cloud

Mangan ese Dioxide Chargin g → Above the Flash Point of Solvent → No Complet e Blanketi ng → Un Safe Conditio n

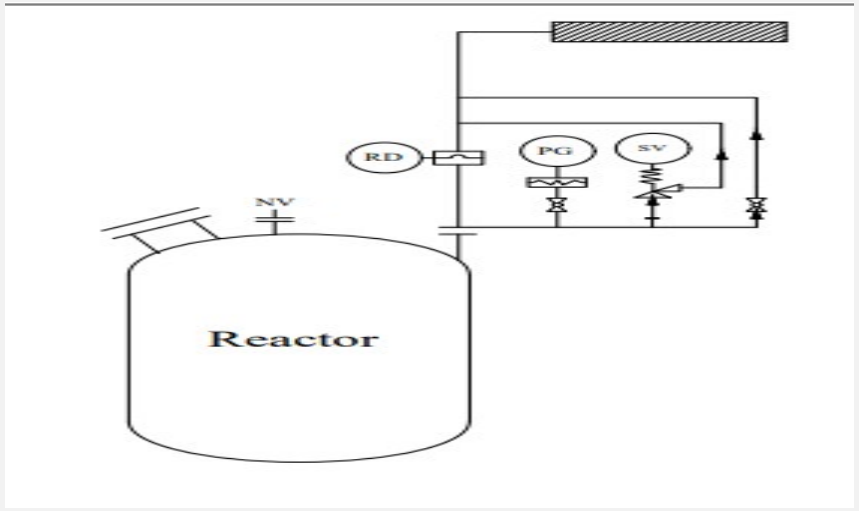


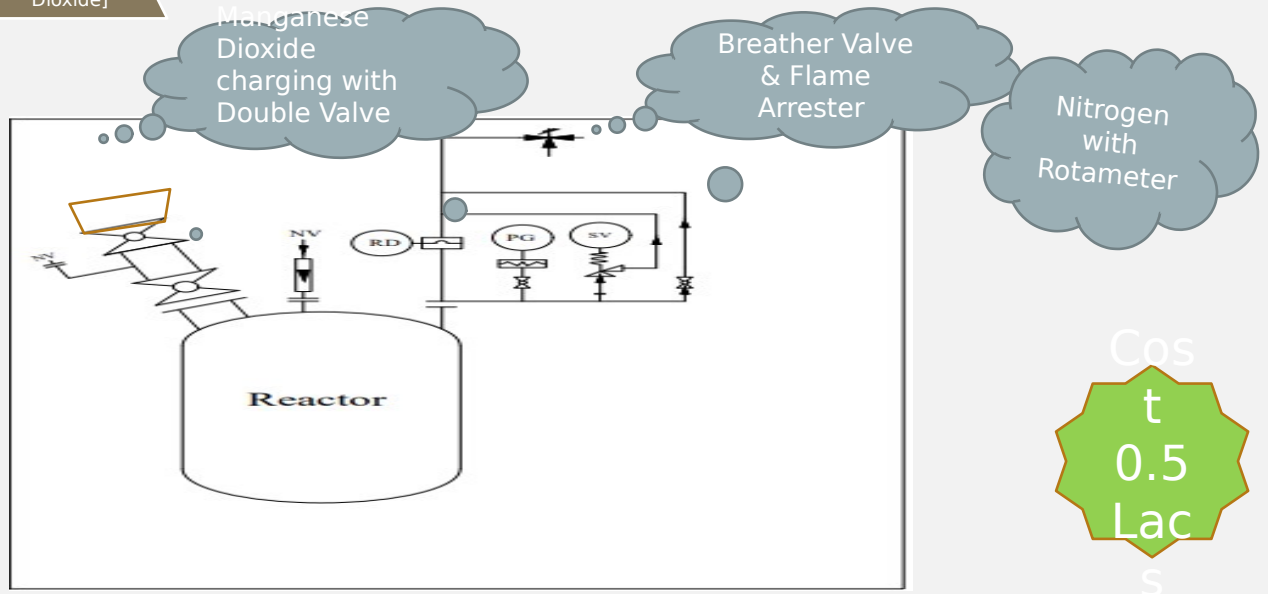
Opportunity :

- Double Valve system to charge the Manganese Dioxide in Close condition.
- Provision of Breather Valve with Flame arrester in vent manifold to keep 200mmwc Positive nitrogen Blanketing during the material charging.
- Reducing the charging temperature from 30-35 deg to less than 10 deg to

char ne flas ethanc eg]

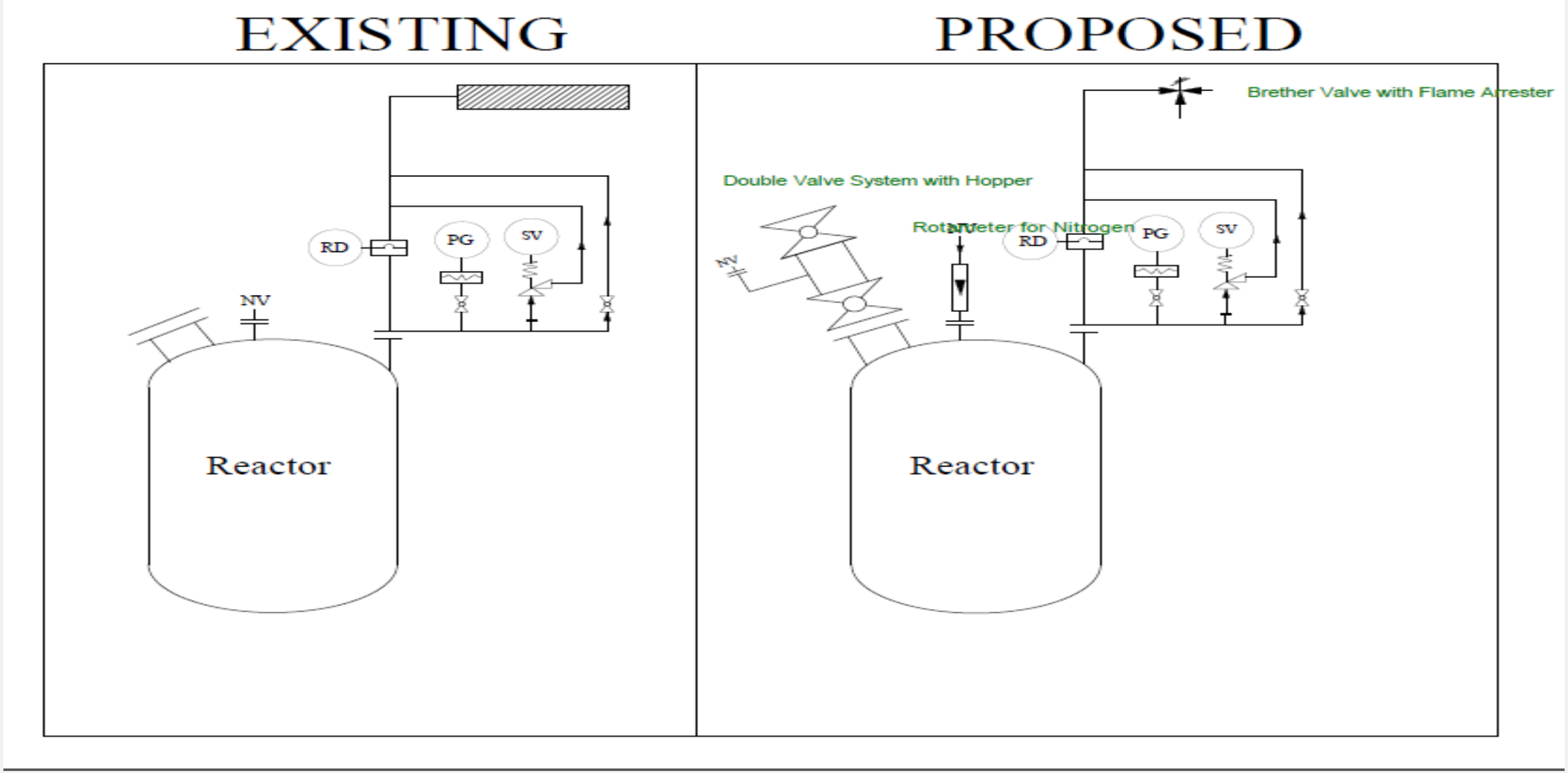
Manganese Dioxide Charging → Less than Flash Point of Solvent → Nitrogen Positive Atmosphere → Safe Handling





Cos t 0.5 Lac s

Existing and Proposed P&ID for Manganese Dioxide Charging



MATURITY CURVE FOR PROCESS ENGINEERING TEAM @ MANUFACTURING UNIT

Establishment phase

- Build human Capital
- Establishing base line performance
- Establishing guidance/direction
- Establishing governance
- Establishing lab infrastructure

Performance phase

- Improvement against base line.
- New technology introduction.
- Design standards
- Site capacity enhancement & trouble shooting.
- Strengthening utilities.
- Improvement in site safety.
- Strengthening ETP
- Support repeat campaigns.

Excellence

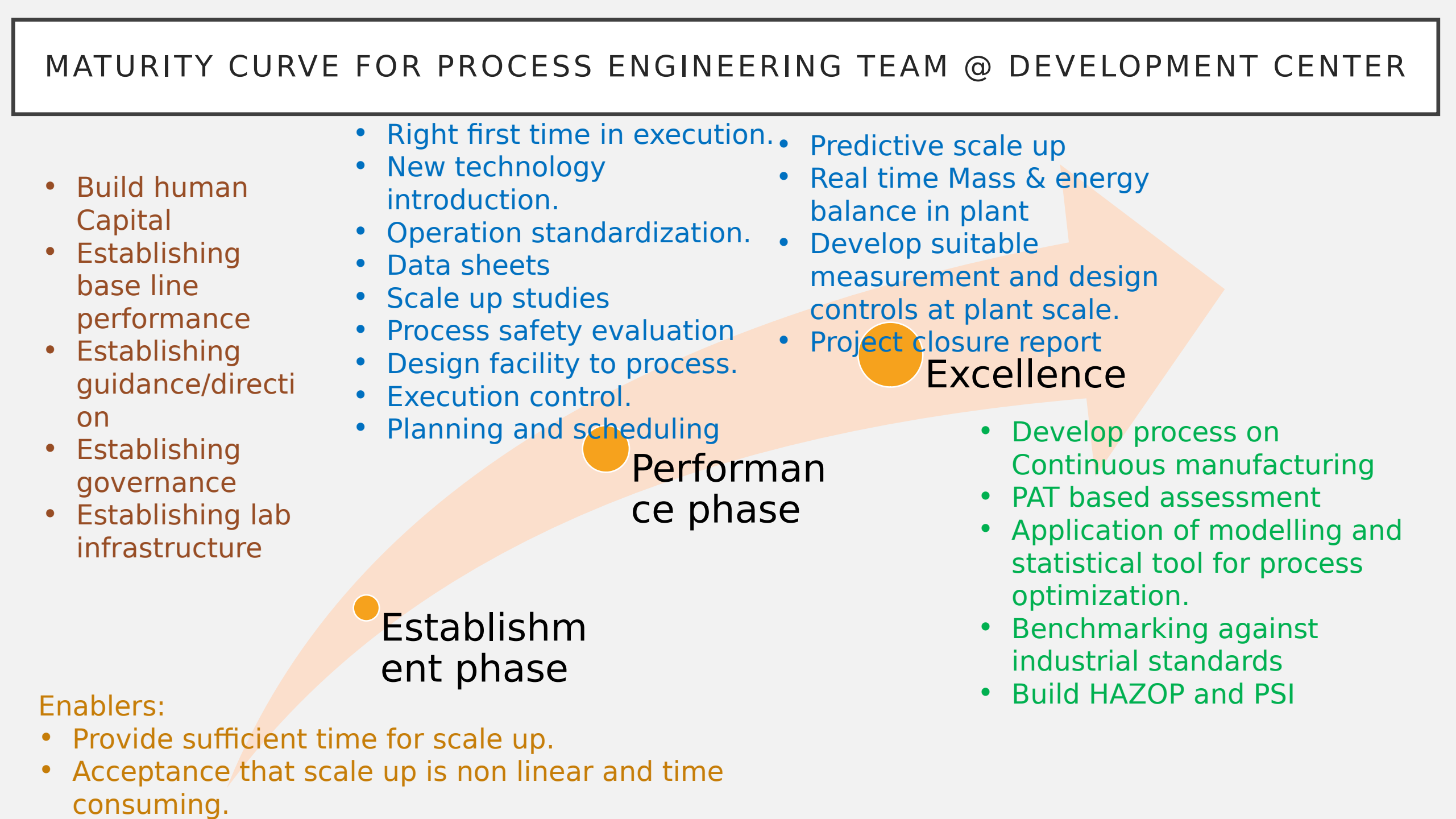
- Support customer request for Particle engg/polymorph challenges/other Physical properties challenges.
- Support new product execution/ Custom service business

- Continuous manufacturing
- Mechanization and automation
- Industry 4.0
- Data driven decisions
- Bench marking against industrial standards
- Safety & quality culture.

Enablers:

- Assimilation and acceptance.
- Understanding what to expect.
- Initiatives owned and driven by site leaders.

MATURITY CURVE FOR PROCESS ENGINEERING TEAM @ DEVELOPMENT CENTER



- Build human Capital
- Establishing base line performance
- Establishing guidance/direction
- Establishing governance
- Establishing lab infrastructure

- Right first time in execution.
- New technology introduction.
- Operation standardization.
- Data sheets
- Scale up studies
- Process safety evaluation
- Design facility to process.
- Execution control.
- Planning and scheduling

- Predictive scale up
- Real time Mass & energy balance in plant
- Develop suitable measurement and design controls at plant scale.
- Project closure report

- Develop process on Continuous manufacturing
- PAT based assessment
- Application of modelling and statistical tool for process optimization.
- Benchmarking against industrial standards
- Build HAZOP and PSI

Enablers:

- Provide sufficient time for scale up.
- Acceptance that scale up is non linear and time consuming.

CONCERNS

Development:

- Sufficient time for execution is not been provided for T&V. The projects drag to almost to final delivery dates during development. This is leading to exceptions while executing T&V.
- The attempt during development is always to address purity. There is less attempt made to address effluent or process intensification.
- Still relying on OFAT approach. This can lead to blind spots
- Enough emphasis is not given to HPLC monitoring. The optimization is done using starting material absence rather then overall impurity profile. This is leading to complex work up incase of higher impurity formation.
- Material attributes are not in control. Materials from different source and quality is brought into picture during development. This is leading to complications during development.

Manufacturing:

- There is a complex interpretation for GMP. This is leading to unnecessary activities and delays.
- We are spending energy in discussing how to an break egg. The decisions on a miniscule issue is discussed at several levels. This is leading to withdrawal tendency at execution level.
- Data logging system is happening by force. It is not voluntary today.
- There is resistance to adopt good practices.
- Material source is unknown some times.
- Monthly/fortnight production planning is not shared for new products. Hence, there is no agreed production plan between TSD and Mfg.
- Delivery supersedes quality/compliance & safety.
- Few sites carry TSD as partners.
- There is no clear ownership driven through TSD. The old practices are prevailing over.

Technical Services Department, Labs-01

TSD Targets/Goals for FY 24

- **Capacity Enhancement or Release by 10% on Total KL Days**
- **Reduction / Recovery & recycling the Solvent by 10% on Actual consumption**
- **Implementation of New Technology - 02 No's to optimize the Operational cost**
- **Implementation of CIP's in coordination with R&D**
- **Continous improvements on commerical Products**
- **Reduction in Effluent by 10% on actual**

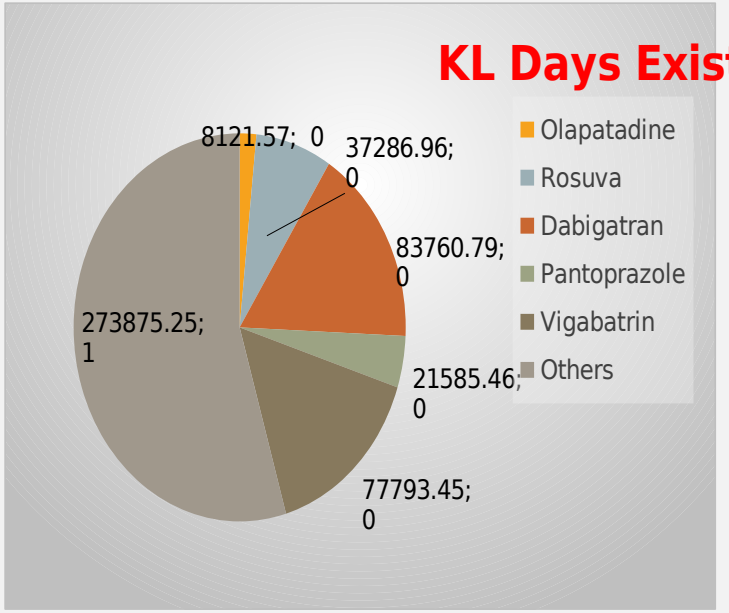
Operational excellence

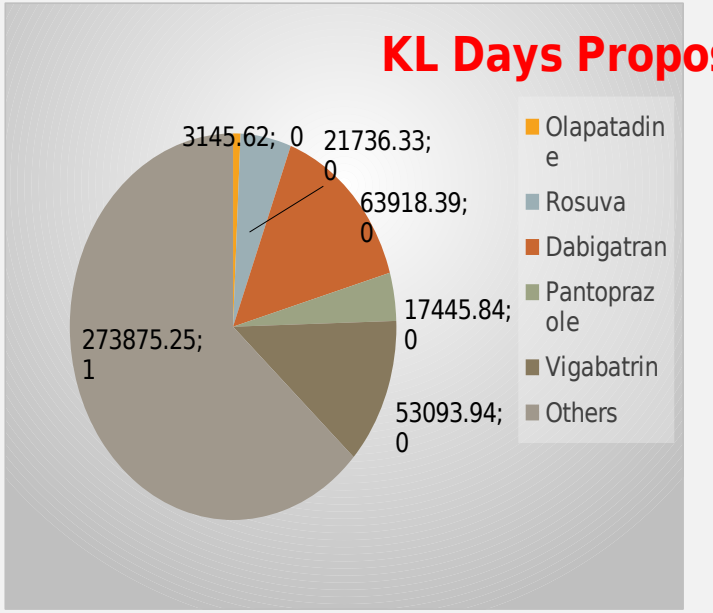
Targets for FY 24 - Capacity Enhancement or Release by

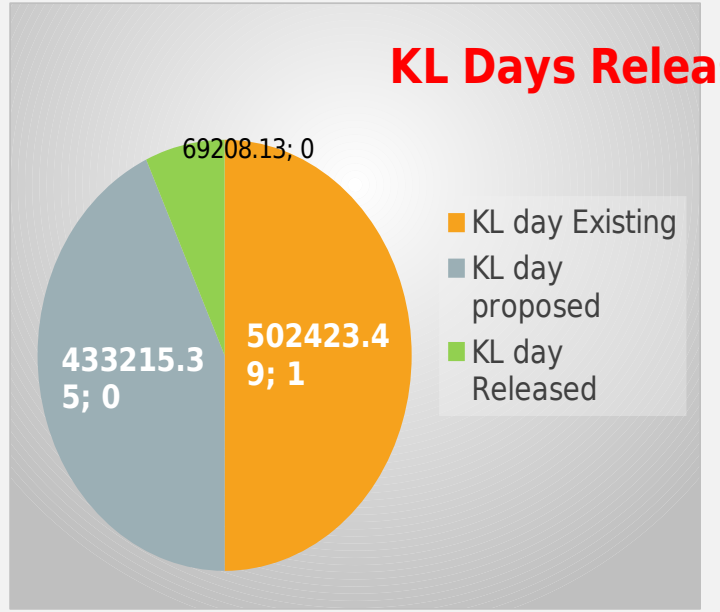
Products	Incremental, MT	Incremental, %	Target Date
Rosuvastatin Calcium	7.8 to 12.0	53%	Dec'23
Pantoprazole	4.5 to 7.0	55%	Oct'23
Vigabatrin	2.4 to 3.2	33%	Mar'24
Dabigatran	2.4 to 4.5	87%	Mar'24
Olapatadine	0.1 to 0.5	400%	Oct'24

Total Plant volume	1352	KL
Total operational days	300	Days
KL Days @ Unit-01	405600	KL days
Support from Other	96,823	KL days
Net KL Days	5,02,423	KL days

Top 06 Molecules Capacity.xlsx







Note: Net release at MSNL-01 will be about 69208 KL Days >> 230 KL >> 115 Cr. In phase manner

Targets for FY 24 --- Solvent

Improveme

A	Solvent reduction @ source
B	Solvent vapour loss reduction
C	Solvent recovery % improvement
D	Solvent recycle implementation

Solvent Name	KL/ Month
Acetone	364
Ethyl Acetate	354
Methanol	323
MDC	295
IPA	262
Toluene	226
THF	106
Others	169
Total	**2098***

Total saving of 11.3 Cr.

Avg Price considered as 45 Rs/L

❑ **Reduction in Solvent consumption by 10%**

Cat - A

- Reduction by1%
- Tentative savings- 0.6 Cr

Cat - B

- Reduction by 3%
- Tentative savings-

Cat - C

- Reduction by 1%

Cat - D

- Reduction by 6%

Cat-A :

- **Re-use of solvent used for bed formation.**
- **Volume optimization based on TLC.**
- **Volume optimization based on soluability.**
- **Elimination of Purifications**

Cat-B :

- **Relook on condenser utility.**
- **Vent condenser.**
- **Insulation to tank.**
- **Filling of water in collection tank (imm.)**
- **Utility flow assessment.**

Cat-C :

- **Segerations of strems.**
- **Column packing.**
- **Condenser sizing**

Solvent consumption.xls

Cat-D : Reuse till n-1 stages

- **Olapatadine--- DCM, THF**
- **Pantoprazole--- DCM & Acetone**
- **Dabigatran ---- Acetone**
- **Vigabatrin---- THF**

Targets for FY 24 --- New Technology

New Technology trials:

- Particle size reduction studies ----- Homogenizer, flow cell .
- Advanced Filtration Equipments ------ Vertical pressure filter, Plate & frame filter press, Rotary vacuum filter, Bag filters for Product or spent salt...
- Advanced Drying Techniques ----- Spherical dryer, Paddle drier (RVPD) for drying time cycle optimization's.
- Nox filters, carbon pads (impegrated) for absorption of Nitrites & amines inorder to control Nitrosoamines.
- Continous Extraction techniques ------ Static mixture with decanter (In-house technology), LLE (RDC or ACE).
- Advance Solvent recovery techniques ----- Per-evaporation or Pressure swing Adsorption (THF recovery for Grignard).
- Continous distillation techniques ----- FFE/RFE, Shortpath for distillation times optimization.
- Controlled addition techniques----- Metering pumps, Rotameters, Dosing pumps for anti solvent crystallization's during scale-up
- Solid chargeing's ------- AODD pumps, Powder transfer system (PTS) for solid charging in safe mode.Closed sampling system for high temperature.

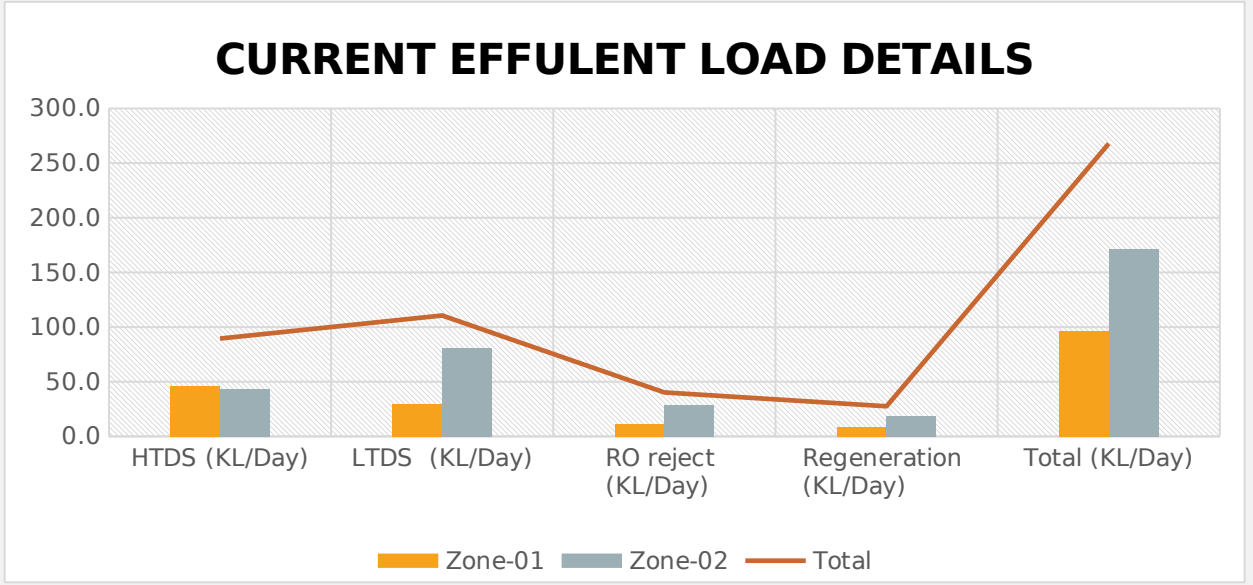
Targets for FY 24 --- Effulent Reduction

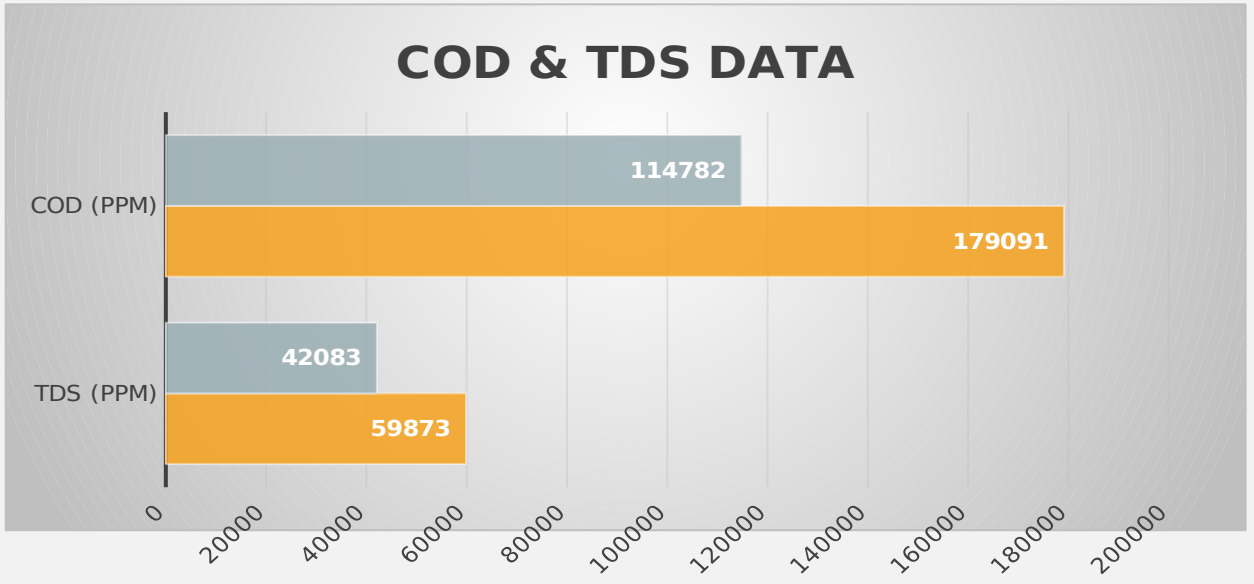
- **Reduction in Effulent load by 10%**
- **Reduction in COD by 10%**

A	Segeration of HTDS & LTDS streams @ Source
B	Solvent recovery from Aqueous streams before it goes to ETP
C	Re-use or re-cycle of Aqueous streams

- **Savings would be about 2.2 Cr**

ETP data.xlsx





Status & Way Forward

Projects Completed So Far

Capacity Enhancements

Release by 10000 KL Days (33 KL) >> ~ 16 Cr. Annu. Savings

Products	Achieved MT	Capex
Pantoprazole	4.5 to 6.5	No investment
Alufuzosine.HCl	0.5 to 1.0	0.75 L (03 rounded Cartridge)
Olapatadine	0.1 to 0.14	0.15 L (line modification)
Rosuvastatin Calcium	7.8 to 9.5	32.0 L (Vacuum pumps)
Finasteride	0.2 to 0.6	No investment

ovement >> ~ 4.2 Cr. Annualized Savings

- ❖ Vinyl Bromide yield improved by 4% (Vapour column & Vent condenser modifictaion).
- ❖ Right selection of filtration equipment has reduced the operation time by 50%.

nprovement & New Techn. >> ~ 1.2 Cr. Annualized Savings

- ❖ Nox Filters & Homogenizer trials ---- U/Installation & progress
- ❖ Alternative vendor for micron filters with better cost (3M)---- Saving 4000 Rs/MF
- ❖ Vertical pressure filter trilas completed.
- ❖ Static mixture with decanter (In-house technology)

Total saving Till date : ~24 Cr.

Solvent Recovery

Solvent recycle >> ~ 2.2 Cr. Annualized Savings

- DCM recycled @ Olapatadine (OPE-2 & OPH-1 stages)--- Required facility for DCM distillation.
- Acetone recovery from Dabigatram ML's & sent for job work.
- Isopropyle Acetate recovery established as POC at lab scale.

COD Reduction >> ~ 0.5 Cr. Annualized Savings

Note: Due to facility constrine on hold for time being

- A Stream of Acetone + water diverted from ETP to reduce the COD.
- Acetone is recovered & aqueous stream is pumped to ETP.

COD (particular stream):

- ❑ Before distillation: 2,90,000 ppm
- ❑ After distillation: 1,38,000 ppm

- **Reduction in COD by 50%**
- **Need CAPEX: 2.0 Cr**

Effulent Reduction

Projects In Pipe-line

Capacity Enhancements

Products	Target MT
Pantoprazole	7.0 to 9.0
Vigabatrin	2.2 to 3.2
Olapatadine	0.14 to 0.5
Rosuvastatin Calcium	9.5 to 12.0
Dabigatran	2.2 to 4.5

New Technology

- Spherical drier planned in 1st week of Aug'23
- FFE/Short path for distillation
- Flow cell for crystallization (PSD)
- Evaluation of Impregnated Carbon pads ---
  - For nitrites & amine removal
  - Avoid handling of loss carbon --- Gives yield improvements
- Air ionoizer
- Auto samplers for high temeprature reactions.

Solvent Recovery

- 16 Reactors were identified for vent loss minimization
  - Phase-01 Capex approved for 05 reactors modification u/Progress
- De-hydration (PAS or Per-evap.) U/evulation for THF--- Trials planned
- Acetone recycle in Dabigatran ----- User trial planned with Distilled acetone
- DCM & Acetone reuse in Panto ---- Pilot trial @ 5.0 Kg scale planned

Effulent Reduction

- Identification of high COD streams
- Improving the ETP effeciency by diverting high COD & TDS streams
  - To avoid solvent loss u/vacuum charging PO to be released.

Yield & Other Improvements

- Working along with the R&D for improvements in below products.
  - Olapatadine yiled improvement.
  - Pantoprazole ML's recycling--- Yield improvement & solvent recycle
  - Finistride ---- Drying elimination in between purifications.
  - Phytonadione---- Scale-up with right yield & quality
- Trouble shootings in ongoing commerial molecules

Thank you!

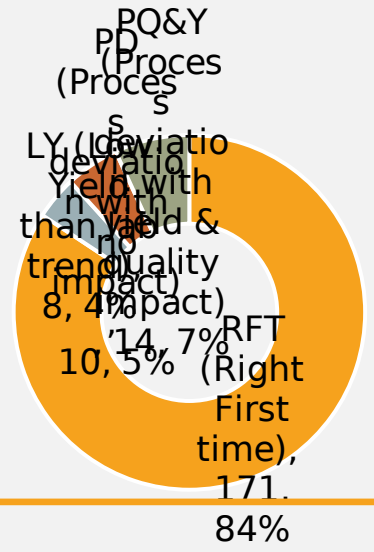
Technical Services

Department, R&D

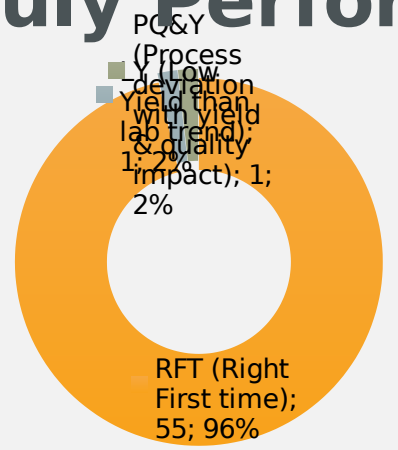
Center

NEW PRODUCT PERFORMANCE

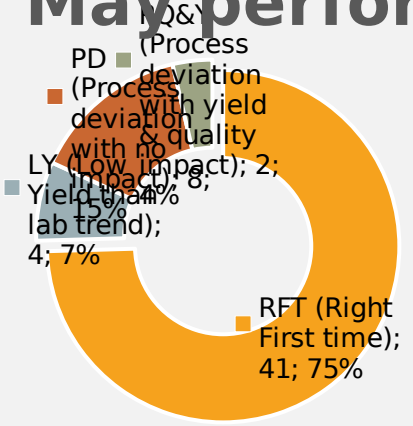
Performance until April


PQ&Y (Process deviation with yield & quality impact); 1; 2%
PD (Process deviation with no impact); 2; 5%
LY (Low deviation with yield & quality impact); 1; 2%
Yield than lab trend); 4; 7%
RFT (Right First time); 171. 84%

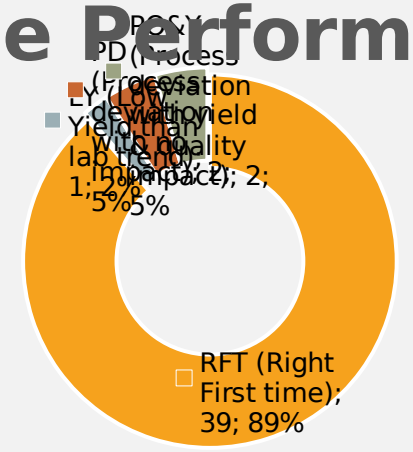
July Performance



May performance


PQ&Y (Process deviation with yield & quality impact); 1; 2%
PD (Process deviation with no impact); 2; 5%
LY (Low deviation with yield & quality impact); 1; 2%
Yield than lab trend); 4; 7%
RFT (Right First time); 41; 75%

June Performance


PQ&Y (Process deviation with yield & quality impact); 1; 2%
PD (Process deviation with no impact); 2; 5%
LY (Low deviation with yield & quality impact); 1; 2%
Yield than lab trend); 1; 2%
RFT (Right First time); 39; 89%

TSD INITIATIVES FOR PROCESS INTENSIFICATION AND OPTIMISATION

Scale-down approach for negative data

- Mixing / Agitation, %Occupancy and type of agitator.
- Identification of critical material attribute that could vary at scale.
- Structured approach to understand the SD and SI parameter interactions.

- Acalabrutinib maleate reaction dilution / mixing
- Fosfomysin raw material PCl3
- HBr acetic acid in Isavocanazonium
- Acetic acid addition in Bisaprolol stage
- Agitator selection in Belumosudil

Right facility to execute CPP

- Secondary heating / cooling utility for sensitive reactions
- Identifying critical equipment set-up well before TT.
- Controlled storage / powder handling areas for critical molecules.

- MEG for heating at 93±2°C in Remigepant sulfate
- Dehumidifier set-up for Fosfomysin
- Cold storage for Isavocanazonium instead of Dry ice

Predictive Scale-up Approach

- Standardized data generation at lab for all the unit operations
- Baseline data generation for filtration and drying operations to predict the process performance at plant scale.
- FMEA approach to be used for standardization of unit operations at plant

- Bulk density (BD) and Tapped density (TD) measurement.
- Preliminary image analysis with Microscope to understand the Morphology.
- Standardised rules for selection of filter based on Hausner ratio

Safety emphasis

- Process Safety evaluation (RC and Powder characteristics) to define operating boundaries.
- Avoiding dry distillations in the process to eliminate safety risk due to decomposition.

- Improve facility to address problems/ risks posed with emissions from process
- Reducing the environmental impact
- Precautions to avoid hazards due to powder handling

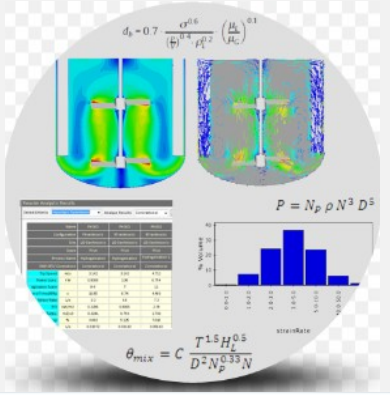
PROCESS ENGINEERING LAB AND COLLABORATION

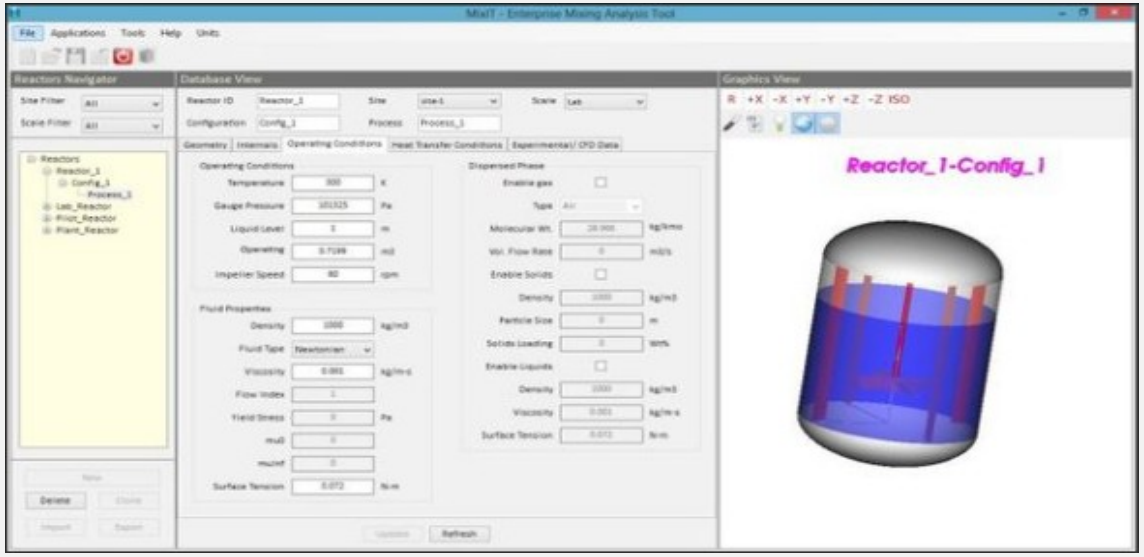
- Standardisation of practices for scale-up by conducting experiments in cylindrical reactor (matching Power / unit volume).
- Process Engineering lab for building capability for study and data generation for the unit operations involved.
- Reaction, Crystallisation and filtration are some of the unit operations for which data generation to be done in PE lab.

Cylindrical reactor set-up with chiller

Pocket Filter for Filtration studies

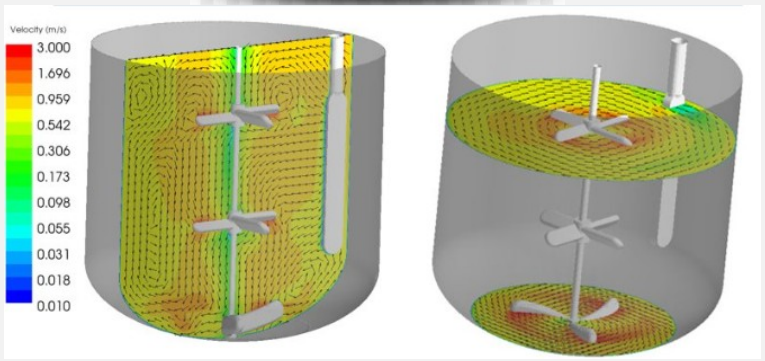
Low flow rate pumps for addition of reagents / solvents





MIXIT

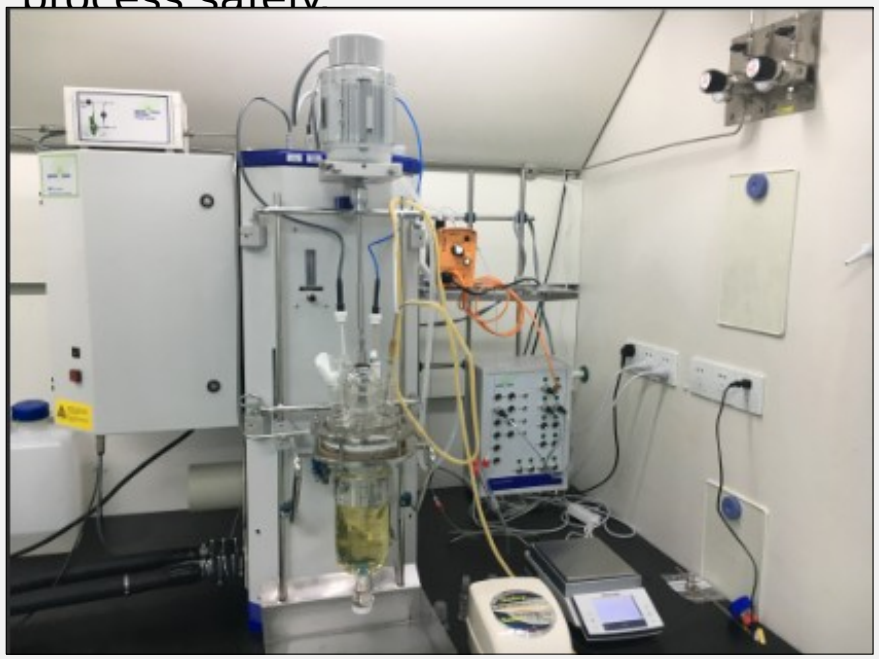
Simulation Software



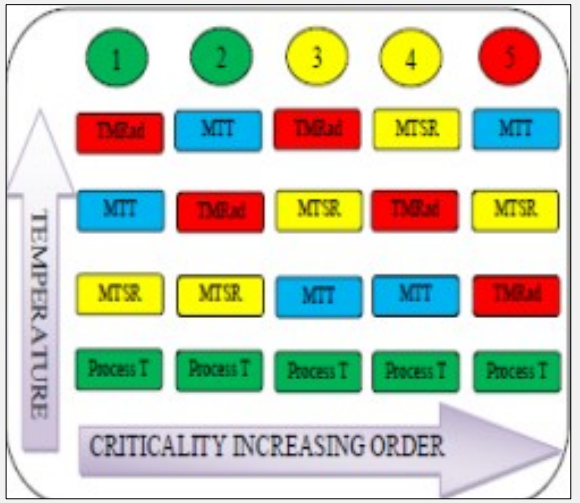
PROCESS SAFETY AND THERMAL RISK ANALYSIS

- No data generation in practise in terms of Process Safety to evaluate the risk in the following conditions:
  - Exothermic reactions / conditions – Uncontrollable temperature rise and (or) Release of gases.
  - Dry distillation – Exposure to higher skin temperatures for longer hours leading to decomposition.
  - Powder handling – Exposure to higher stress conditions

- RC1e equipment will help in understanding the adiabatic temperature rise in the process resulting due to exothermic release and provides thermal data to design / select the right facility / utility for executing the process safely



Reaction calorimetry Set-up



STOESSEL'S Criticality index

MIE Apparatus

CONCERNS DURING DEVELOPMENT & SCALE-UP

- Effluent from processes are high and are the major contributors to the overhead cost today.
- Data is not generated in a orderly fashion in lab, which is leading to blind spot. .

Lab experimentation with DoE

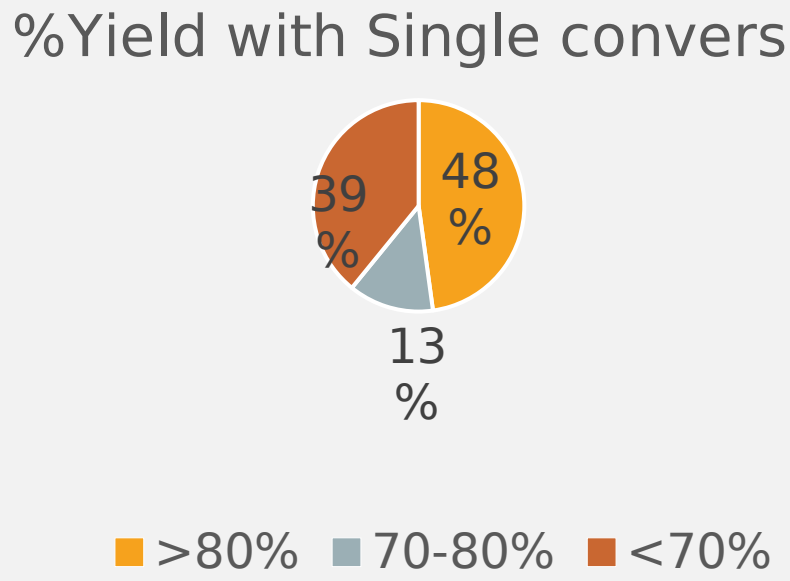
Lab experimentation with OFAT method

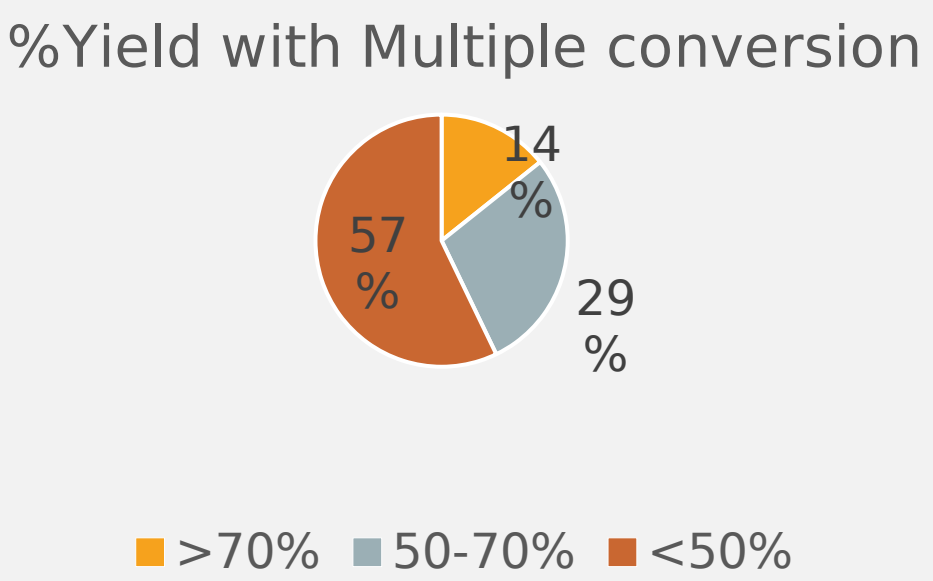
RUN	Factors			Maintenance Time	REGX 4 content from TLC	Purity
	Methanol (in vol)	NaOH (eq)	Temp (°C)			
Run 1	3	1	50	24 hrs	~80%	-----
Run 2	7	1	50	24 hrs	~50%	-----
Run 3	3	3	50	24 hrs	~60%	----
Run 4	7	3	50	**12 hrs**	**< 2%**	98.05%
Run 5	3	1	80	24 hrs	~70%	----
Run 6	7	1	80	24 hrs	~40%	----
Run 7	3	3	80	5 hrs	< 2%	76.94%
Run 8	7	3	80	**2 hrs**	**< 2%**	86.19%
C1	5	2	65	12 hrs	< 2%	94.92%

Parameters conclusion with minimum experimentation

- Ambiguity in understanding the parameters impacting the lower performance of the process at lab and thereby no concrete method to control the same in plant.
- Finger printing of impurities are not happening during optimization. This is mainly occurring due to adoption of TLC for optimization instead of HPLC.
- Non-standard equipment design at plant making it difficult to scale-up from kilo-lab.
- Practices are different from plant to plant in terms of execution / equipment handling.

CONCERNS DURING DEVELOPMENT AND SCALE-UP





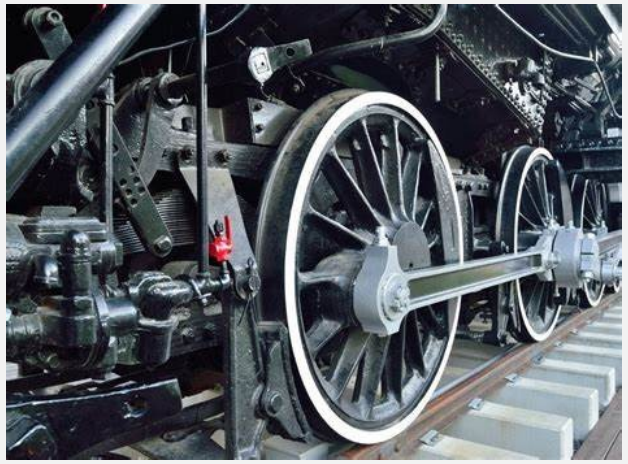
- More than 50% of products have yield below 85%. (> 85% is industry standard for single conversion.)
- Good number of stages have yields below industry standards in multi conversion synthesis.

Thank you!

PILLARS FOR RELIABILITY & REPRODUCIBILITY

Process Design & control

Equipment/ facility Design & control

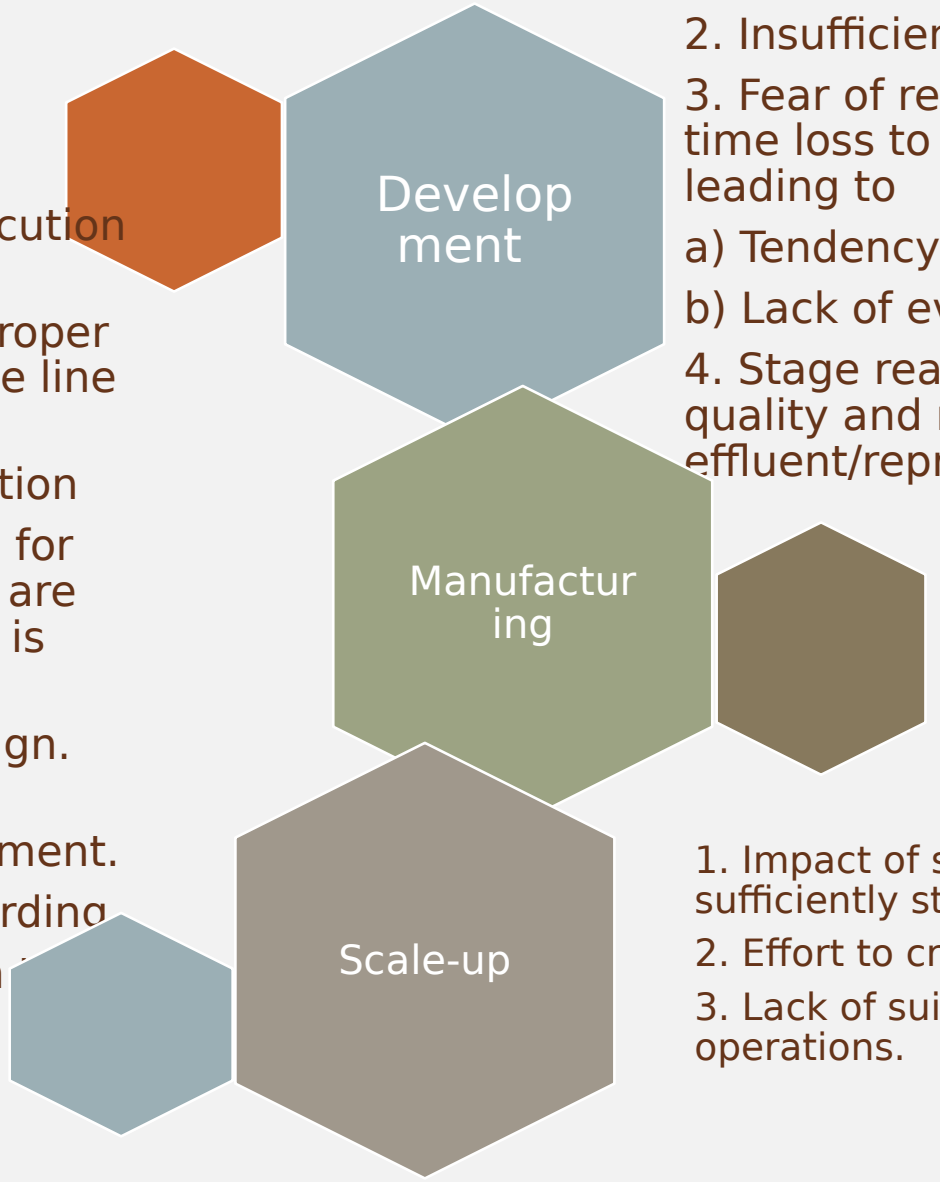


Incident reporting and analysis

Translating scientific knowledge to operating language

One of the fact is the deaths due to road accidents are than the death due to corona

PRACTISES IMPACTING PROCESS PERFORMANCE AT SCALE



1. Difference in Physical execution vs document – leading to

a) loss of information b) improper data recording c) lack of base line for improvement.

2. Lack of online documentation

3. There is no time allocated for facility preparation- batches are executed where ever facility is available.

4. Inefficient equipment design. (PNF/leaf /agitators/ dryers)

5. Inefficient utility management.

6. No provision for data recording

7. Change in batch size from to validations.

1. Lack of mechanistic understanding

2. Insufficient analytical methods

3. Fear of reporting incidents (on account of time loss to investigation closure) – this is leading to

a) Tendency to take exception path.

b) Lack of evidences to bring improvement

4. Stage readiness is evaluated only on quality and not on effluent/reproducibility/safety etc.

1. Impact of scale dependent parameters are not sufficiently studies during lab development.

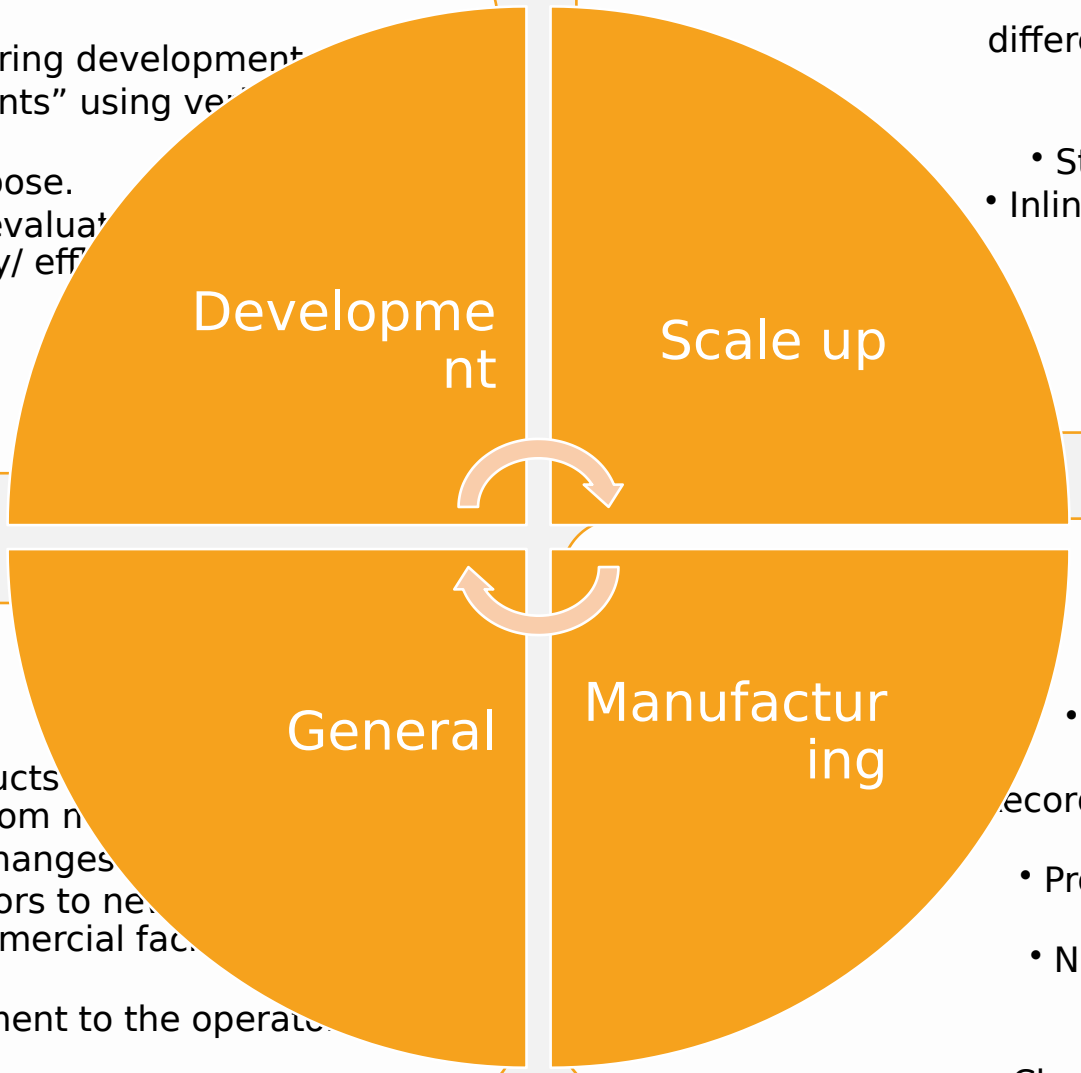
2. Effort to create right facility is not in practice.

3. Lack of suitable equipment for challenging unit operations.

Lack of risk management – leading to exception during crisis.

PROPOSAL FOR COURSE CORRECTION

- Extensive stress studies.
- Inclusion of scale down studies during development
- Test the “demonstration experiments” using ve
  analytical techniques.
- Buy right equipment for right purpose.
- The process readiness should be evaluat
  matrices such as safety/ scalability/ eff
  consumption etc.



- Extensive sampling and testing at different process points during execution.
- Creating right facility with right equipment.
- Standardization of equipment design.
- Inline measurements for better controls.

- Give a kitty amount for new products
  improvement in facility. (apart from n
- Give free hand to engg to bring changes
- Dedicate the block or set of reactors to ne
  (mapping new products into commercial fac
  compromise).
- Provide better operating environment to the operat
  (clean environment /safety)

- Online documentation of executed batches.
- ecording of right temperature, pressure and other process parameters.
- Production planning and allocation of facility in advance.
- Non usage of refurbished solvents in DMF stages.
- Upkeep of utilities.
- Change the inferior equipment designs and replace with new ones.
- Operational discipline & inbuilt safety